PCT/AU03/01729

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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003100262 for a patent by JUROX PTY LTD as filed on 07 April 2003.

WITNESS my hand this
Twentieth day of January 2004

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AUSTRALIA

Patents Act 1990

JUROX PTY LTD

COMPLETE SPECIFICATION
INNOVATION PATENT

Invention Title:

Stable carprofen composition

The following statement is a full description of this invention including the best method of performing it known to us:-

STABLE CARPROFEN COMPOSITION

Technical Field

This invention relates to non-steroidal anti-inflammatory drug (NSAID) compositions and in particular to such compositions where the NSAID is presented in the form of a solution for use in warm blooded animals, such as dogs.

Background Art

There are a number of NSAID's that are known to be useful for the treatment of inflammation and pain in animals such as dogs. These NSAID's are typically used in treating postoperative pain associated with soft tissue and orthopaedic surgeries as well as for the relief of pain and inflammation associated with osteoarthritis.

One such useful NSAID is carprofen. This drug is a member of the class of drugs that includes indomethacin, naproxen and ketoprofen. Chemically, carprofen is 6-chloro-α-methyl-9H-carbazole-2-acetic acid.

Whilst carprofen has been found to be a very effective therapeutically, in order to maintain an acceptable stability profile, it must be formulated in dosage forms such as tablets where solvents are largely excluded. For administration to humans, such dosage forms do not present a barrier to use. However, for administration to non-human animals, solid dosage forms are not well tolerated and are generally difficult to administer.

It would therefore be desirable if carprofen could be presented in a non- solid dosage form thereby allowing the substance to be more easily administered.

The present inventors have recognised this limitation on the use of carprofen and accordingly have sought to provide compositions that are stable and solvent-based for ease of administration to warm-blooded animals, especially dogs.

In the disclosure that follows, any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia before the priority date of each claim of this application.

Moreover, throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

Disclosure of Invention

The present inventors have achieved stable solvent-based compositions of carprofen through the finding that certain solvent combinations with carprofen result in formulations that are stable and are suitable for oral administration to animals.

Accordingly, in a first aspect, the present invention is directed to a stable solvent-based composition comprising:
a therapeutically effective amount of carprofen;
one or more polyols;
one or more stablising agents; and optionally,
one or more co-solvents.

In a second aspect, the present invention is further directed to a method of treating pain and/or inflammation in an animal, the method comprising administering to the animal a therapeutically effective amount of carprofen which is solubilised in a composition which comprises:
one or more polyols;
one or more stabilising agents; and optionally,
one or more co-solvents.

In a third aspect, the present invention is still further directed to the use of a composition which comprises:
one or more polyols;
one or more stabilising agents; and optionally,
one or more co-solvents,
to stabilise carprofen and to facilitate the oral administration of a therapeutically effective amount of carprofen to a warm-blooded animal.

Carprofen is included in the compostion in an amount of 1 to 500g/L, preferably 20 to 50g/L. At these concentrations, an appropriately therapeutically effective amount of the composition may be administered to an animal.

One or more polyols are included in the composition and these may be selected from the group consisting of propylene glycol, glycerol, sorbitol, solid polyethylene glycols, liquid polyethylene glycols and mixtures of the foregoing. Broadly the polyols may be incorporated in an amount of from 20 to 998g/L. Preferably they are used in an amount of from 700 to 998g/L. In the case of sorbitol, it is usual to provide the sorbitol as a 70% w/v aqueous solution. In addition, in order for the polyethylene glycols to be liquid, there molecular weight will generally be in the range of about 300-

600. However, potentially solid polyethylene glycols could be used in combination with one or more suitable co-solvents.

Amongst the stabilising agents that may be used are antioxidants. These include α tocopherol and salts thereof, ascorbic acid and salts thereof, methoxyphenol and derivatives thereof, trihydroxybenzoate and derivatives thereof, hydroquinone and derivatives thereof, methyl phenol and derivatives thereof and sodium metabisulfite. Generally these stabilising agents are regarded as antioxidants. In addition, benzyl alcohol may be used as a stabilising agent. Such stabilising agents may be used singly or in combination in a total amount of 0.1 to 50 g/L, preferably 10 to 20g/L.

Optionally, one or more co-solvents may be included in the compositions of the invention. One co-solvent that may be used is ethanol. If a co-solvent is used, the amount is typically up to 500g/L, preferably 10 to 300g/L.

Although the compositions of the invention are solutions of carprofen, it will be readily appreciated that the viscosity of such solutions may be modified to produce compositions that are enhanced so as to be, for example, more paste like or in the form of a gel.

To produce the compositions of the invention, the carprofen may be dissolved in polyol along with the stabilising agent. If a co-solvent is used, it may be added following the dissolution of the carprofen and stabilising agent.

The compositions according to the present invention are for oral administration to warm-blooded animals, particularly dogs. For successful administration, these compositions must be palatable to the animal to be treated.

Modes for Carrying out the Invention

In order to better understand the nature of this invention, a number of examples will now be described.

Example 1

Ingredient	Amount
Carprofen	25g
Butylated hydroxytoluene	1g
Ethanol	100mL
Polyethylene glycol 400	qs 500mL

Example 2

Ingredient	Amount
Carprofen	10g
Butylated hydroxyanisole	2g
Sorbitol 70% aqueous solution	qs 500mL

Example 3

Ingredient	Amount
Carprofen	10g
Butylated hydroxytoluene	1g
Sorbitol 70% aqueous solution	100mL
Propylene glycol	qs 500mL

Example 4

Ingredient	Amount
Carprofen	25g
Butylated hydroxyanisole	2g
Polyethylene glycol 400	400mL
Ascorbic acid	5g
Ethanol	qs 500mL

Example 5

Ingredient	Amount
Carprofen	20g
Propylene glycol	qs to 1L
Benzyl alcohol	10g

Example 6

Ingredient	Amount
Carprofen	50g
Butylated hydroxytoluene	5g
Ethylene glycol	qs to 1L

In Examples 1-6, each composition was prepared by dissolving the carprofen in the polyol. The stabilising agent was then dissolved and if appropriate, co-solvent was added to complete the formulations. The availability of all of the ingredients used is set out in Table 1.

Table 1 – Ingredient Availability

Ingredient	Available from
Carprofen	Pacific Resources International Pty Ltd
Butylated hydroxyanisole	Bronson & Jacobs
Polyethylene glycol 400	Bronson & Jacobs
Ascorbic acid	Bronson & Jacobs
Ethanol	CSR
Butylated hydroxytoluene	Bronson & Jacobs
Sorbitol	Bronson & Jacobs
Propylene glycol	Bronson & Jacobs
Benzyl alcohol	Bronson & Jacobs
Ethylene glycol	Bronson & Jacobs

The stability of Examples 3 and 6 was evaluated by storing samples for various times at 30 and 40°C. The results of these stability trials are set out in Tables 2 and 3 from which it can be seen that the samples were stable for the time tested. By comparison, an example tested that did not incorporate a stabilising agent, had degraded to an unacceptable level of carprofen after 1- 3 months storage at 30°C.

Table 2 – Stability Evaluation of Example 3

Storage Time (months)	Carprofen (g/L) Temperature 30°C	Carprofen (g/L) Temperature 40°C
Initial	19.8	19.8
3	19.9	20.2
6	20.1	19.9
9	19.7	20.3

Table 3 – Stability Evaluation of Example 6

Storage Time (months)	Carprofen (g/L) Temperature 30°C	Carprofen (g/L) Temperature 40°C
Initial	21.0	21.0
3	21.0	21.0
6	20.6	20.6
12	20.0	19.8

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A stable solvent-based composition comprising:
a therapeutically effective amount of carprofen;
one or more polyols in an amount of from 20 to 998g/L;
one or more stabilising agents in an amount of from 0.1 to 50g/L; and
one or more co-solvents in an amount of from 0 to 500g/L.

2. The carprofen composition according to claim 1 wherein the one or more polyols are selected from the group consisting of propylene glycol, glycerol, sorbitol, solid polyethylene glycols and liquid polyethylene glycols, preferably liquid polyethylene glycols, and mixtures of the foregoing; the one or more stabilising agents are selected from the group consisting of α tocopherol and salts thereof, ascorbic acid and salts thereof, methoxyphenol and derivatives thereof, trihydroxybenzoate and derivatives thereof, hydroquinone and derivatives thereof, methyl phenol and derivatives thereof, sodium metabisulfite and benzyl alcohol.

3. The carprofen composition according to claim 1 or claim 2 wherein the carprofen is in an amount of from 1 to 500g/L, preferably 20 to 50g/L.

4. The carprofen composition according to any one of claims 1 to 3 wherein the one or more polyols are in an amount of from 700 to 998g/L, the one or more stabilising agents are in an amount of from 10 to 20g/L and the one or more co-solvents are in an amount of from 10 to 300g/L.

5. Use of a composition which comprises:
one or more polyols;
one or more stabilising agents; and optionally,

one or more co-solvents,
to stabilise carprofen and to facilitate the oral administration of a therapeutically effective amount of carprofen to a warm-blooded animal.

Dated this 4th day of April 2003

Jurox Pty Ltd
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ABSTRACT

A stable solvent-based composition of carprofen is disclosed. The composition comprises a therapeutically effective amount of carprofen, one or more polyols; one or more stablising agents; and optionally one or more co-solvents. Polyols such as propylene glycol, glycerol, sorbitol, polyethylene glycols may be used together with stablising agents such as antioxidants and benzyl alcohol.